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The Effect of Testosterone on Metabolic Syndrome and Type 2 Diabetes

Abstract

Background: Metabolic syndrome (MetS) and diabetes type 2 (DM2) are increasing in incidence in the United States. A recent study found that roughly 34% of the adult population meets the criteria for metabolic syndrome. Patients with metabolic syndrome were found to have a 3 fold higher incidence of MI, stroke and CHD compared to patients without MetS. They were also more likely to develop DM2. Men with metabolic syndrome or DM2 also have a higher incidence of hypogonadism. It is estimated that 37.8% of men >45 years are hypogonadal. Multiple studies have established a link between hypogonadism and metabolic syndrome and the next step is to evaluate if raising a man's testosterone levels back to physiologic norms has any benefit in the treatment of metabolic syndrome or DM2.

Methods: A comprehensive review of the literature was performed using the data bases: CINAHL, ovid - Medline, EBMR Multifile, Web of Science, PubMed and Google scholar. This produced a number of studies and the following exclusion criteria were applied to limit the search. Exclusion criteria: studies in another language, studies not using testosterone as a therapy, studies on patients who did not have MetS or DM2, studies on women, studies using non-hypogonadal men, studies with a sample size less than 15.

Results: This resulted in three studies which were evaluated for this review. In all three studies evaluated, there was a greater improvement in patients treated with testosterone therapy than placebo. In the 52 week study of diet and exercise compared to diet and exercise plus testosterone, 62.5% of testosterone patients no longer met the criteria for MetS and 87.5% of them reached a HgbA1c goal of <6.5%. The two other studies, which only had a treatment phase of 3 months, also had promising results. Both studies demonstrated a drop in fasting glucose and insulin levels which corresponded to a decrease in HgbA1C. Patients in all three studies had improvements in BMI and waist to hip ratio. There were no adverse outcomes reported in any of the studies.

Conclusion: Testosterone replacement therapy appears to be beneficial in more places than the bedroom. We have yet to discover all effects testosterone replacement has on the body, but initial studies are promising. Preliminary studies demonstrate that testosterone replacement in hypogonadal men has a greater benefit than risk. It is currently recommended to test men with symptoms of hypogonadism, especially if they have concurrent MetS or DM2. Returning a man's T level back to physiologic norms can improve MetS and potentially slow its progression to DM2.

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The Effect of Testosterone on Metabolic Syndrome and Type 2 Diabetes

Alison Quammen



A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

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Faculty Advisor: Mary Von PA-C

Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow
PharmD, OD

Biography

Alison Quammen spent most of her childhood in Montana where she developed a love of the outdoors and a sense of adventure. Alison attended Montana State University – Billings where she graduated with honors receiving a B.S in biology with chemistry minor. During her junior year in college she was accepted to participate in a research project in Oslo, Norway. This experience sparked her enthusiasm for international travel. After graduating college she spent the next five years traveling to different parts of the world. She funded her travels by working summers as a wilderness river guide in Idaho. One of her regular clients on the river offered her a job on a private yacht in the Caribbean, where she spent a total of 13 months. Working on the boat funded her next trips to Africa, where she fell in love with the landscape and the people and vowed to return to help. Medicine had always been in the grand picture she had for herself, but as she was approaching 30, plans needed to be revised and implemented. She decided that Physician Assistant School would fit into her adventurous lifestyle quite well. She is currently finishing off the last grueling couple of months of PA school at Pacific University Oregon and trying to figure out where her next adventure is going to take her.

Abstract

Background: Metabolic syndrome (MetS) and diabetes type 2 (DM2) are increasing in incidence in the United States. A recent study found that roughly 34% of the adult population meets the criteria for metabolic syndrome. Patients with metabolic syndrome were found to have a 3 fold higher incidence of MI, stroke and CHD compared to patients without MetS. They were also more likely to develop DM2. Men with metabolic syndrome or DM2 also have a higher incidence of hypogonadism. It is estimated that 37.8% of men >45 years are hypogonadal. Multiple studies have established a link between hypogonadism and metabolic syndrome and the next step is to evaluate if raising a man's testosterone levels back to physiologic norms has any benefit in the treatment of metabolic syndrome or DM2.

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Results: This resulted in three studies which were evaluated for this review. In all three studies evaluated, there was a greater improvement in patients treated with testosterone therapy than placebo. In the 52 week study of diet and exercise compared to diet and exercise plus testosterone, 62.5% of testosterone patients no longer met the criteria for MetS and 87.5% of them reached a HgbA1c goal of <6.5%. The two other studies, which only had a treatment phase of 3 months, also had promising results. Both studies demonstrated a drop in fasting glucose and insulin levels which corresponded to a decrease in HgbA1C. Patients in all three studies had improvements in BMI and waist to hip ratio. There were no adverse outcomes reported in any of the studies.

Conclusion: Testosterone replacement therapy appears to be beneficial in more places than the bedroom. We have yet to discover all effects testosterone replacement has on the body, but initial studies are promising. Preliminary studies demonstrate that testosterone replacement in hypogonadal men has a greater benefit than risk. It is currently recommended to test men with symptoms of hypogonadism, especially if they have concurrent MetS or DM2. Returning a man's T level back to physiologic norms can improve MetS and potentially slow its progression to DM2.

Keywords: metabolic syndrome, diabetes mellitus type 2, testosterone, therapeutics, and hypogonadism

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To Lincoln; well it has been a bumpy ride these last couple of years, but we have hung on. I have not always been able to articulate how grateful I am for your support, but know it has meant the world to me.

Lastly to Roscoe, my loyal brown dog. Thank you for helping me stay sane over the last two years. You were always there with a toy in your mouth and body wriggling uncontrollably to meet me at the door after a very long day in the classroom or at the clinic. You knew when I needed a break from the hours spent at my desk and would squeak your toy in my face until I took that much needed break. Most of all thank you for reminding me that it is the simple things in life that bring you the most happiness.

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List of Abbreviations

ASA – American Society of Andrology
ASCVD – Atherosclerotic Cardiovascular Disease
BMI – Body Mass Index
CHD – Coronary Heart Disease
DM2 – Diabetes Mellitus type 2
EAA – European Academy of Andrology
EAU – European Association of Urology
HDL – High Density Lipoprotein
HgbA1C – Hemoglobin A1C
HRT – Hormone Replacement Therapy
IDF – International Diabetes Federation
IM – Intramuscular injection
ISA – International Society of Andrology
ISSAM – International Society for the Study of Aging Male
LDL – Low Density Lipoprotein
LOH – Late Onset Hypogonadism
MetS – Metabolic Syndrome
MI – Myocardial Infarction
NS – Normal Saline
PSA – Prostate specific antigen
TG – Triglycerides

The Effect of Testosterone on Metabolic Syndrome and Type 2 Diabetes

BACKGROUND

Obesity is becoming a major epidemic as Americans become less active and adopt a more sedentary lifestyle. The WHO estimates that globally, there are more than 1 billion overweight adults, with at least 300 million of them being obese.¹ This epidemic is currently taking a huge toll on our health care system and it is predicted to only get worse. It is estimated that obesity accounts for 2-6% of total health care costs in developed nations, but the true cost is likely much higher, as all obesity related illnesses are not currently taken into account.¹ Obesity is a risk factor for the development of diabetes mellitus type 2 (DM2) and a leading component of the metabolic syndrome (MetS).

The constellation of symptoms that is known as MetS increases a person's risk of developing atherosclerotic cardiovascular disease (ASCVD) and DM2.² The general features of MetS as defined by the Adult Treatment Panel III (ATP III) are: abdominal obesity, atherogenic dyslipidemia, elevated triglycerides, small LDL particles, low HDL cholesterol, raised blood pressure, insulin resistance (\pm glucose intolerance), a prothrombotic state and a proinflammatory state.³ (Table 1) The prevalence of MetS has increased over the last few years. The Third National Health and Nutrition Examination Survey was performed from 1988-1994 and showed that 22% of US adults met the ATP III guidelines for MetS.⁴ A more recent study⁵ conducted from 2003-2006 showed that 34% of the population 20 years and over met the criteria for MetS. That is a 12% increase

in just over 10 years! The incidence of MetS appears to be positively correlated with increasing age, and even more dramatically, with increasing BMI.⁵ Abdominal obesity appears to be the most common risk factor, with 30% of overweight males and 65% of obese males meeting the criteria.⁵ Incidence also increased with age, 41% of males 40-59 years of age and 52% of males aged 60 years or older also met the criteria.⁵ As our society grows older and larger, it is going to be essential to find a way to prevent MetS from progressing into DM2 and other health conditions. One of the associations that is currently being studied is that between MetS and/or DM2 and hypogonadism.⁶⁻¹¹

There are two main types of hypogonadism, primary and secondary. Primary testicular failure results in low testosterone levels, impaired spermatogenesis, and elevated gonadotropin levels. Secondary testicular failure is associated with low or low-normal gonadotropin levels and low testosterone levels.¹² It has recently been proposed that there is a third type of hypogonadism where gonadotrophin levels may be low to normal. This type is associated with chronic illnesses including obesity, metabolic syndrome and DM2 among others.¹³

There is much controversy about the specific testosterone level that constitutes hypogonadism and there is currently no agreed upon standard lab value that designates it. Because the effects of testosterone are widespread on the body, designating only a lab value to define an abnormality is limiting. Current recommendations are, that late onset hypogonadism (LOH), is a clinical and biochemical syndrome associated with advancing age; and characterized by symptoms and a deficiency in serum testosterone levels below the reference range of a young healthy adult male.¹⁴

Recent studies¹⁵ have looked at the prevalence of LOH in the male population. They defined hypogonadism as a total testosterone (TT) < 300 ng/dl and using this reference they found that roughly 38.7% of men >45 years are hypogonadal. This extrapolates to around 13.8 million men in the US.¹⁵ With that large of the population having this condition, you would think more men would be receiving testosterone replacement already. There is still reluctance on the health care providers' part to prescribe testosterone because it was thought that it could induce prostate cancer, but studies seem to be showing that it has no effect on the prostate.¹⁶

There does seem to be an association between the incidence of hypogonadism and other conditions. It was found that there was the greatest association of hypogonadism with body mass index (BMI), the odds of having the condition were 2.74x more likely in a male with a BMI > 25kg/m² than a male with a BMI of < 25kg/m².¹⁵ Patients with chronic illnesses such as hypertension (HTN), hyperlipidemia, and DM2 also had a significantly higher likelihood of having co-morbid hypogonadism.¹⁵

Several studies have been done that have established a link between hypogonadism and metabolic syndrome and/or DM2.⁶⁻¹⁰ With obesity being the number one risk factor for both MetS and hypogonadism, Jones proposed a mechanism of action that links the two. He proposes that visceral fat has high aromatase activity which metabolizes testosterone into estradiol, the more visceral fat, the more the aromatase. The testes would not be able to produce enough testosterone to compensate for the loss. This fall in testosterone levels leads to a greater activity of lipoprotein lipase causing an increased storage of triglycerides and proliferation of adipocytes, thus increasing insulin resistance. Normally the body would release more luteinizing hormone to stimulate the

testes to produce more testosterone, but that process is blocked by the estradiol and adipocytokines.¹³ According to his theory one exacerbates the other and continues a vicious cycle.

Laaksonen et al⁹ found that men with a total testosterone level in the lower third of the range were 3.5-fold more likely to have metabolic syndrome than men with concentrations in the upper third. Hypogonadal patients were found to have a significantly higher BMI, larger waist to hip circumference, higher insulin concentrations, elevated triglycerides and an increased HOMA value as compared to eugonadal men.¹⁷ Those characteristics are all components of MetS. Diabetic patients have lower total and free testosterone levels in comparison with the rest of the sample population and their testosterone levels were inversely related to waist circumference.¹⁰ The Telecom Study,¹¹ performed on healthy adult men, found that plasma testosterone levels negatively correlate with age, fasting plasma glucose, 2-h plasma glucose, fasting plasma insulin and BMI. These studies all demonstrate that if you have one condition, you are much more likely to have the other, so where do we go from here? The next logical step is to evaluate if there is any benefit to increasing a man's testosterone level back to physiologic normal.

METHODS

A comprehensive review of the literature was performed using the data bases: CINAHL, ovid - Medline, EBMR Multifile, Web of Science, PubMed and Google scholar. The keywords used for the search were: metabolic syndrome, DM2, testosterone, therapeutics and hypogonadism. This produced a number of articles on each database;

therefore the following inclusion and exclusion criteria were used to narrow the search to the appropriate studies. Inclusion criteria: studies involving hypogonadal men with either DM2 or MetS or both, using T as a treatment for those disorders. Exclusion criteria: studies in another language, studies not using testosterone as a therapy, studies on patients who did not have MetS or DM2, studies on women, studies using non-hypogonadal men, studies with less than 15 people.

RESULTS

After applying these criteria, three studies remained. Of these studies, only one was a double blind placebo controlled study,¹⁸ the other two were singly binded¹⁹ and an open label study.²⁰ All the studies were performed in the last eight years in Europe.

Testosterone Replacement Therapies Effect on Insulin Resistance

Kapoor et al¹⁸ conducted a double blind placebo-controlled crossover study. The trial was for a total duration of 7 months with two treatment phases. The participants were randomized into either treatment or control, this phase lasted three months, there was a washout period of one month and then the groups switched. All subjects were men older than 30 years with DM2 and hypogonadism. A total of 27 men were randomized.¹⁸

The treatment consisted of a 200mg testosterone IM injection every two weeks for 3 months. The placebo group received 0.9% normal saline injection every two weeks for 3 months. All concomitant oral hypoglycemic, anti-hypertensive and lipid-lowering medications were permitted and continued throughout without any dose adjustments. The patients on insulin were allowed to make dose adjustments to prevent hypoglycemia.¹⁸

The following were the statistically significant results when compared to placebo: total testosterone and bioavailable testosterone levels increased in treatment group (P

0.001), fasting glucose decreased by 1.58 (P 0.03), total cholesterol decreased by 0.4 (P 0.03), HOMA index was reduced 1.73 (P 0.02) and HbA1C was reduced 0.37 (P 0.03). Waist circumference decreased by 1.63 (P 0.03) and waist/hip ratio decreased by 0.03 (P 0.01). Of the 10 patients on insulin, 5 patients reduced daily dosages by a mean of 7 units. There were no changes in PSA, BP, LDL, HDL or TG.¹⁸

The Effect of Diet and Exercise Plus Testosterone on Metabolic Syndrome

Heufelder et al¹⁹ evaluated the effects of adding testosterone gel in addition to diet and exercise in the treatment of DM2 and MetS. This study was a single blind study where the study personnel, but not the participants, were blinded. It was a randomized trial lasting for 52 weeks of 32 hypogonadal males with MetS or newly diagnosed DM2. Participants were randomized to diet and exercise only or diet and exercise plus testosterone treatment (50mg gel applied daily). The participants were not taking any oral antihyperglycemic agents or insulin. All the participants were instructed to have 3 meals a day that consisted of a low glycemic load, were low in saturated fats and rich in omega-3, and they were instructed to attempt to eat 25% fewer calories per meal. For the exercise portion of the trial, they were advised to walk for 30 minutes and do 15 minutes of muscle building exercise with weights or elastic strings three times per week. Staff contacted participants at least twice a week to encourage adherence to the treatment. The compliance with D&E was 100%.¹⁹

Both arms of the study had improvement in all areas evaluated, but the testosterone treatment group had a greater benefit. In the treatment arm, patients testosterone levels increased from 10.5 to 15.4 nmol/L, HbA1C decreased by 1.3%, fasting plasma glucose decreased from 7.9 to 6.1 mmol/L and insulin levels decreased

from 113.2 to 40.2 pmol/L. All testosterone patients reached HgbA1C goal of <7% and 87.5% reached <6.5%. 62.5% of patients no longer matched the International Diabetes Federation (IDF) criteria for MetS. Waist circumference declined in both groups, but more so in the testosterone group and PSA did not increase in either treatment arm.¹⁹

The control group also saw benefits from this study. With only diet and exercise, participants' testosterone levels increased slightly from 10.4 to 11.2 nmol/L, HgbA1C decreased by 0.5%, fasting plasma glucose decreased from 8.3 to 6.6 mmol/L and their insulin levels decreased from 116.9 to 60.2 pmol/L. Only 40.4% of the diet and exercise patients reached the goal HgbA1C levels <7%, and none reached <6.5%, but 12.5% of patients no longer met the IDF criteria for MetS.¹⁹

Testosterone, Type 2 Diabetes and Androgen Deficiency

Boyanove et al²⁰ performed an open-label, randomized, no-treatment controlled study of 48 men with DM2 and total testosterone in the lower 1/3 of normal range for young adults (<15.1 nmol/L). There were 24 men in the treatment group who received oral testosterone undecanoate, 80 mg in the morning and 40 mg at night for three months. This was compared to 24 control subjects who received no treatment or placebo.²⁰

The treatment arm resulted in body weight being reduced by 2.66% (P <0.05) and BMI by 3.2%. Waist/hip ratio decreased by 3.96% (P <0.05) and body fat decreased by 5.6% (P <0.05). Fasting, postprandial and mean daily blood glucose values dropped significantly (P <0.05) and HgbA1C had an absolute decrease of 1.8% (P <0.05). There were no significant changes in systolic or diastolic BP or in serum total cholesterol. All symptoms of androgen deficiency (nervousness, insomnia, fatigue and decreased libido)

were significantly improved in the treatment group. As expected, total serum testosterone increased in the treatment group and there were no adverse events reported during the study.²⁰

DISCUSSION

The results of these three studies, while limited, are promising. There is clearly a link between low testosterone levels and increasing levels of insulin, glucose and BMI¹¹ in the aging male. Finding new ways to combat these issues will lead to a healthier society.

Effects on Glycemic Control

One of the most harmful and difficult aspects to manage in DM2 or MetS are glucose levels. The damage which elevated glucose levels cause on all organ systems in the body takes a huge toll on a person's health and is usually irreversible. However just a small decrease in circulating glucose can have substantial health benefits in that it can slow the progression of the disease, but reaching a target HgbA1C goal of < 7% takes making major lifestyle changes and is very therefore difficult.²¹

Testosterone replacement therapy improved HgbA1C in all the studies. Participants in the Heufelder et al¹⁹ study all met the HgbA1C goal of <7% with 87.5% of the testosterone group reaching a goal of <6.5%. None of the control group were able to reach a goal of <6.5%. Another study²⁰ showed a drop in HgbA1C from an average of 10.4 to 8.6% after 3 months of treatment with testosterone, placebo only decreased from 10.3 to 9.9%. A drop in HgbA1C from 10-8% lowers the average circulating glucose from 240 mg/dl to 183 mg/dl.²² (Table 2) The third study¹⁸ also demonstrated a drop in HgbA1C as a consequence of a statistically significant drop in fasting glucose levels, P

0.03. Kapoor et al¹⁸ also had a reduction in insulin dosage in the treatment arm of the study. Of the 10 patients on insulin, five reduced their daily dosage by a mean of 7 units. Reducing circulating glucose levels can slow or prevent the progression of MetS to DM2.

The ISA, ISSAM, EAU, EAA, and ASA have issued guidelines¹⁴ in regards to testosterone replacement and diabetes within the last couple of years. They have concluded that serum testosterone levels should be measured in men with DM2 with symptoms suggestive of testosterone deficiency (Level 2b, Grade A) (Table 3). They go on to say that in men with hypogonadism and diabetes and/or metabolic syndrome, the testosterone treatment for traditional hypogonadal symptoms may have other unproven benefits on their metabolic status (Level 2a, Grade B).¹⁴

Body Composition

According to the National Health Statistics Reports,⁵ abdominal obesity is the number one risk factor for developing metabolic syndrome. Diabetic men have a higher BMI and waist to hip ratio than nondiabetics⁸ and hypogonadal patients have a significantly higher BMI and waist to hip ratio than eugonadal men.¹⁷ Both hypogonadism and metabolic derangements are associated with an increasing waist line.

Visceral fat appears to be more metabolically active than subcutaneous fat and it drains directly into the liver which exposes it to more free fatty acids, thus increasing hepatic insulin resistance.¹³ These are the factors that make reducing abdominal fat so important to stopping the progression of MetS to DM2. A waist to hip ratio of >0.9 in men seemed to have a greater correlation to MetS and subsequent risk factors for cardiovascular morbidity and mortality than a BMI > 30 kg/m² did.²³ After only 3 months of treatment with testosterone, waist to hip ratio decreased from 1.01 to 0.97 in one

study²⁰ and 1.02 to 0.99 in the other study.¹⁸ The 52 week study¹⁹ also showed an improvement in waist to hip ratio, but did not specify how much of an improvement there was.

One of the most promising outcomes of all the studies was in the 52 week study¹⁹ where 62.5% of men treated with diet and exercise plus testosterone no longer met the International Diabetes Federation (IDF) definition for MetS, compared to 12.5% of diet and exercise only. This elimination of MetS is important because patients with MetS have a threefold higher likelihood of developing coronary heart disease (CHD), MI, and stroke than patients without MetS. They were also more likely to die within the six year follow up period than patients without MetS.²³

The current recommendation is that in men with hypogonadal values, testosterone replacement improves body composition (Level 1b, Grade A).¹⁴ Testosterone supplementation is by no means a magic bullet, but it does warrant more investigation. As Heufelder et al¹⁹ demonstrated there is significant benefit to the old adage, “move more, eat less” but by replacing a man’s T level back to physiological norms, there is an even greater benefit.

Adverse Outcomes

Hormone replacement therapy (HRT) has been a very controversial topic in the health care field. The controversy has always been with women and there has not been much investigation into male HRT. Preliminary studies appear to be promising, but the possible adverse outcomes must always be examined. The most worrisome outcome would be testosterone therapy inducing prostate cancer or converting subclinical prostate cancer into clinically detectable cancer. A randomized control trial of 41 men¹⁶ looked at

the development of prostate cancer after testosterone therapy. They found that of the 41 men, six developed prostate cancer, four were in the control group and two were in treatment group. Of the studies evaluated today,¹⁸⁻²⁰ none of the participants had any adverse outcomes and there was no increase in circulating PSA levels in the studies that measured it.¹⁹¹⁸

The ISA, ISSAM, EAA and ASA¹⁴ have found that there is no evidence that testosterone treatment will convert subclinical prostate cancer to clinically detectable prostate cancer (level 4, grade C), but there is unequivocal evidence that testosterone can stimulate the growth and aggravate symptoms in men with locally advanced or metastatic prostate cancer (level 2a, grade A). They also suggest that in hypogonadal men >45 years the risks and benefits of testosterone substitution should be discussed and they should be carefully monitored for prostate safety during treatment (Level 3, Grade A).¹⁴ Testosterone replacement therapy is contraindicated in men with prostate or breast cancer (Level 3, Grade A). It is also recommended that men with significant erythrocytosis, untreated obstructive sleep apnea, and untreated severe congestive heart failure not be started on testosterone replacement until co-morbid conditions are resolved.¹⁴

Study Limitations

These were by no means perfect studies. One of the main limitations of these studies was the short duration of treatment. The Heufelder et al¹⁹ study was the longest at 52 weeks with the other studies^{18, 20} only having a treatment phase of three months. The ideal study would run for at least five years of treatment.

There was also discrepancy in how the testosterone was administered. Each study used a different kind of testosterone, one used gel,¹⁹ another IM¹⁸ and the last one used an

oral T.²⁰ Each route of delivery has different absorption rates and can have its own gamut of side effects. In future studies the route of administration of testosterone needs to be standardized.

Only one of the studies was a placebo controlled double blind study,¹⁸ one was an open study²⁰ and the other was only singly blinded.¹⁹ The ideal study is always a double blind placebo controlled study. There were definite limitations to the current studies, but they have established the need for further evaluation.

The ideal study would be a double blind, placebo controlled study of middle aged men with metabolic syndrome, not currently on any treatment, with a study length of 5 years. This study would look at the progression to DM2 in placebo compared to treatment group, effects on the prostate, hyperviscosity, HgbA1C levels, and CV effects. Men in treatment group would have their testosterone levels replaced to physiological norms and would all have the same method of testosterone deposition.

CONCLUSION

There is a clearly defined link between hypogonadism and metabolic syndrome. Replacing a man's testosterone levels back to physiologic norms appears to have many beneficial results. One of the benefits appears to be on metabolic derangements which can lead to DM2. Early research has shown, in hypogonadal men treated with T, a reversal of metabolic syndrome in some,¹⁹ decrease in waist circumference,^{18, 20} improved HgbA1C¹⁸⁻²⁰ and improved fasting insulin levels.^{18, 19} All of these factors, left untreated, increase a man's risk of ASCVD.²³ Improvement of these risk factors can substantially improve a patient's quality and quantity of life.

There are known risk factors to replacing testosterone levels to supraphysiologic levels, but initial studies have shown that replacement to physiologic norms has few side effects.¹⁶ It is currently recommended that in men with DM2 who are displaying symptoms of hypogonadism their testosterone levels are checked.¹⁴ They also state that testosterone replacement may have other unproven benefits on metabolic status and the risks and benefits should be discussed with all men before initiating treatment.¹⁴ The studies evaluated,¹⁸⁻²⁰ appear to show that the benefits of testosterone replacement currently outweigh the potential risks and as with any treatment in medicine informed consent is key.

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TABLES

TABLE 1. Criteria for Clinical Diagnosis of Metabolic Syndrome²⁴

Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Categorical Cutpoints
Elevated waist circumference*†	≥102 cm (≥40 inches) in men ≥88 cm (≥35 inches) in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or On drug treatment for elevated triglycerides‡
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.3 mmol/L) in women or On drug treatment for reduced HDL-C‡
Elevated blood pressure	≥130 mm Hg systolic blood pressure or >85 mm Hg diastolic blood pressure or On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL or On drug treatment for elevated glucose

*To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration.

†Some US adults of non-Asian origin (eg, white, black, Hispanic) with marginally increased waist circumference (eg, 94–101 cm [37–39 inches] in men and 80–87 cm [31–34 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cutpoint (eg, ≤90 cm [35 inches] in men and ≤80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

‡Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking one of these drugs are presumed to have high TG and low HDL.

Table 2—Estimated average glucose²²

A1C (%)	mg/dl*	mmol/l†
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CIs. *Linear regression
eAG (mg/dl) $28.7 \times \text{A1C} - 46.7$. †Linear regression
eAG (mmol/l) $1.5944 \times \text{A1C} - 2.5944$.

Table 3- Level of evidence and grade of recommendation utilized in the recommendations¹⁴

Level Type of evidence

1a - Evidence obtained from meta-analysis of randomized trials

1b - Evidence obtained from at least one randomized trial

2a - Evidence obtained from one well-designed controlled study without randomization

2b - Evidence obtained from at least one other type of well-designed quasi-experimental study

3 - Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies, and case reports

4 - Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Grade Nature of recommendations

A - Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial

B - Based on well-conducted clinical studies, but without randomized clinical trials

C - Made despite the absence of directly applicable clinical studies of good quality

Table 4 – Summary Matrix of Reviewed Literature

Author	Yr. published	Patients/ Population	Intervention	Comparison	Outcome(s)	Study type	Validity (Jadad score)
D Kapoor et al ¹⁸	2006	Men 30 yrs or greater w/ type 2 DM and hypogonadism	IM testosterone 200 mg q 2 weeks x 3 mo	IM saline q 2 weeks x 3 mo	Testosterone replacement improved insulin resistance and glycemic control.	Double blind placebo-controlled crossover study	5/5
Heufelder et al ¹⁹	2009	32 hypogonadal males w/ metabolic syndrome and newly diagnosed type 2 DM	Diet and exercise plus testosterone gel 50 mg qd	Diet and exercise only	Both groups saw an improvement in HgbA1C and the compents of MetS, but an even greater improvement was observed with the addition of testosterone.	Randomized single blinded study	3/5
Boyanov et al ²⁰	2003	48 men with DM2 and serum T levels below the normal range for young adults or in the lower 1/3 of this range.	Oral testosterone undecanoate x 3 mo. 80 mg qam, 40 mg q pm everyday	No treatment	Testosterone treatment improved metabolic control of DM2, decreased visceral obesity and lowered HgbA1C values.	Open-label, randomized, no-treatment controlled study.	2/5

Table 5 – Results Summary

	Kapoor et al ¹⁸		Heufelder et al ¹⁹		Boyanov et al ²⁰	
	Treatment	Control	Ttreatment	Control	Treatment	Control
HgbA1C %	7.28% to 6.91%	7.28% to 7.25%	7.5% to 6.3%	7.5% to 7.1%	10.4% to 8.6%	10.3% to 9.9%
Fasting Glucose mmol/L	7.83 to 7.38	7.6 to 8.73	7.9 to 6.1	8.3 to 6.6	8.0 to 6.0	8.4 to 8.0
Fasing insulin pmol/L	13.68 mIU/l to 11.76 mIU/l	12.37 mIU/l to 12.36 mIU/l	113.2 to 40.2	116.9 to 60.2	Not reported	Not reported
BMI (kg/m ²)	33.28 to 33.62	32.85 to 32.97	Not reported	Not reported	31.08 to 30.08	31.01 to 30.88
W/H ratio	1.02 to 0.99	Not reported	Not reported	Not reported	1.01 to 0.97	1.03 to 1.02